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CASE REPORT

Follicular and epidermal alterations in patients treated with ZD1839 (Iressa), an inhibitor of the epidermal growth factor receptor

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Summary We report the cutaneous side-effects of ZD1839 (Iressa), a new anticancer agent that acts by inhibiting epidermal growth factor (EGF) receptor signal transduction. Three patients receiving ZD1839 developed an eruption consisting of follicular papules and pustules in an acneiform distribution as well as diffuse fine scaling of the skin. Additionally, hair growth abnormalities were noted in two patients. Histologically, a superficial purulent folliculitis and disordered differentiation with focal parakeratosis were seen. The follicular eruption appeared to respond favourably to treatment with tretinoin cream and minocycline. The cutaneous adverse effects of ZD1839 are similar to those of other EGF receptor-targeted agents and result from direct interference with the functions of EGF receptor signalling in the skin.

Key words: acneiform eruption, cutaneous adverse effects, epidermal growth factor receptor, ZD1839 (Iressa)

ZD1839 (Iressa) is an orally active, selective epidermal growth factor (EGF) receptor tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and other host-dependent processes promoting cancer growth.[1–4] EGF receptors are expressed on various cancer cells, as well as on epidermal keratinocytes and other cells residing in the skin. EGF receptor signalling contributes to cancer growth primarily by inducing proliferation, but also by promoting cell migration and angiogenesis.[5] ZD1839 selectively inhibits EGF receptor signal transduction by interfering with binding of adenosine triphosphate to the intracellular tyrosine kinase region of this receptor. It is currently being tested in phase II/III clinical trials in the treatment of a number of solid tumours, in particular non-small cell lung cancer. A number of patients included in these trials and treated with oral ZD1839 250 or 500 mg daily developed a similar cutaneous reaction pattern.

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Case reports

We examined three patients who experienced cutaneous adverse effects during treatment with ZD1839. In all three patients the cutaneous reaction started 5–12 days after initiation of treatment. Patients developed numerous discrete small pustules and erythematous papules confined to the hair follicles distributed over the face, trunk and upper arms. This was followed by diffuse fine scaling of the interfollicular epidermis involving the whole integument, giving a xerosis-like appearance. No patient had nodular or cystic lesions, and notably there was no seborrhoea. The lesions healed without formation of scars. Patients complained of dry skin and mild to severe itching. None used other medications known to trigger or exacerbate acneiform eruptions. In the three patients described, the cutaneous adverse effects did not necessitate reduction of the dose or discontinuation of treatment with ZD1839.

In patient 1, a 59-year-old man treated with either 250 or 500 mg daily (blinded) ZD1839 as

monotherapy, the acneiform eruption began on the face and spread peripherally within weeks to involve the abdomen, forearms and lower legs. Scaling was severe and asteatotic eczema was seen on the legs and flanks. His scalp hair had changed and was curled, fine and brittle. After temporary discontinuation of treatment for reasons other than cutaneous toxicity, the lesions healed without scarring, but reappeared soon after treatment was recommenced. The follicular lesions responded favourably to treatment with emollients and minocycline 100 mg daily.

In patient 2, a 54-year-old woman treated with either 250 or 500 mg daily (blinded) ZD1839 as monotherapy, in addition to follicular papules and pustules, open comedones were present on the chest and back (Fig. 1). After progressive worsening of the eruption during the first 2 weeks of treatment, a spontaneous improvement was noted. As observed in the first patient, the hair was finer, more brittle and curlier, especially on the extremities. She also complained of fragility and easy bruising of the skin. We treated her with tretinoin 0·025% cream, which reduced the development of pustules and comedones, and allowed continued administration of ZD1839.

Patient 3, a 59-year-old man, received ZD1839 500 mg daily in combination with a standard regimen of gemcitabine and cisplatin. The follicular lesions became confluent, forming erythematous macules and plaques studded with pustules on the forehead (Fig. 2). On the upper back both comedones and follicular papules were seen. This patient noticed that the growth of his beard had slowed down during the treatment. Twice daily application of tretinoin 0·025% cream led to improvement of the follicular lesions, but aggravated the scaling of the skin.

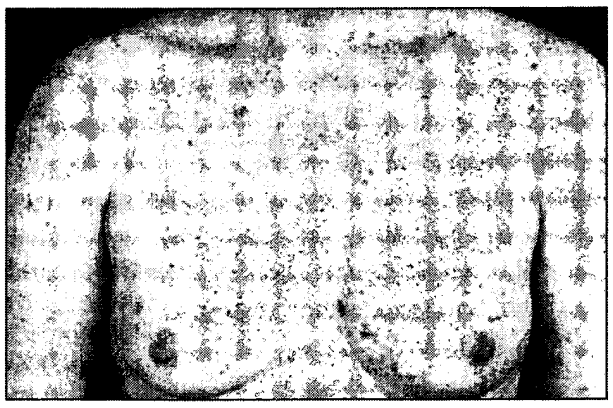

Figure 1. Follicular eruption on the chest of a 54-year-old woman treated with ZD1839 (patient 2).

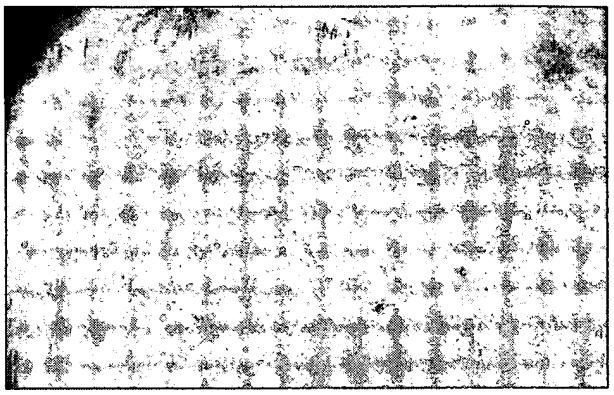

Figure 2. Pustules on an erythematous base as well as scaling of the interfollicular epidermis on the forehead of a 59-year-old man treated with ZD1839 500 mg daily in combination with a standard regimen of gemcitabine and cisplatin (patient 3).

Laboratory investigations

Bacterial and fungal cultures of the pustular contents showed *Propionibacterium acnes* in patient 2 and absence of pathogenic micro-organisms in patients 1 and 3. The total blood count did not show eosinophilia or other alterations in any patient.

Histology

Three skin biopsies taken from pustular lesions of patients 1 and 3 showed similar histological changes. Different stages of a purulent folliculitis were seen. Most follicles were surrounded by an infiltrate composed of lymphocytes and histiocytes. The superficial portion of some follicles was densely infiltrated by neutrophilic granulocytes with partly fragmented nuclei and histiocytes (Fig. 3). The formation of follicular pustules was often accompanied by a remarkable absence of the follicular epithelial lining. In more advanced lesions there was destruction of the follicle with perifollicular granuloma formation, dermal oedema and vasodilatation. The sebaceous glands were relatively small and were not affected by the infiltrate. No micro-organisms were found. The epidermis showed more subtle changes: the stratum corneum had lost its basket-weave appearance, and was thin and compact with varying parakeratosis. There was somewhat irregular epidermal differentiation with slight hypogranulosis, but no evident atrophy.

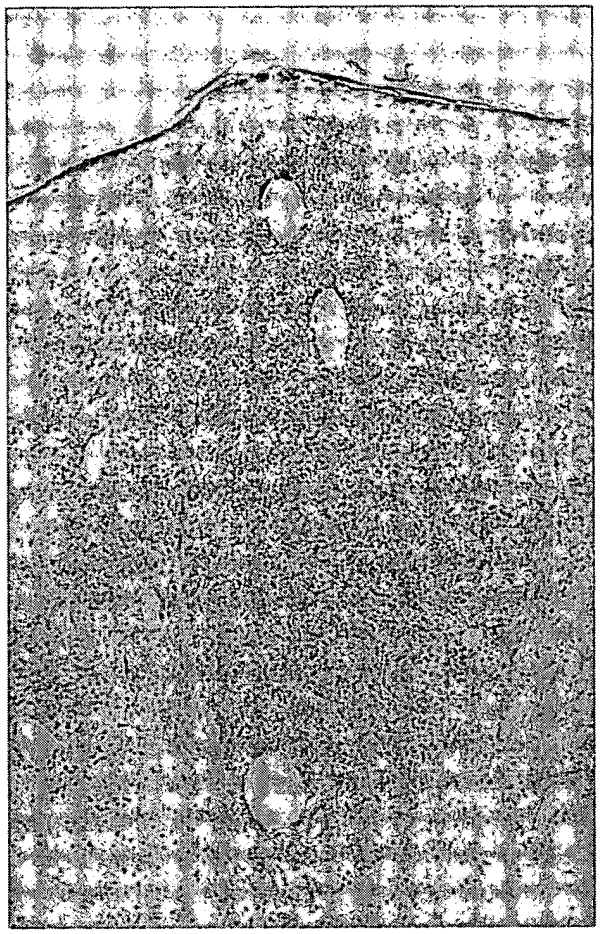

Figure 3. Photomicrograph from a pustule on the back, demonstrating a follicle filled with partly degenerated neutrophilic granulocytes and histiocytes (patient 1; haematoxylin and eosin; original magnification × 10).

Discussion

The skin eruption observed in these patients treated with the EGF receptor inhibitor ZD1839 consisted of follicular papules and pustules in an acneiform distribution and diffuse fine scaling of the skin. Hair growth abnormalities were noted in two patients. Histology of the skin lesions revealed a purulent folliculitis as well as slightly irregular epidermal differentiation. Similar cutaneous adverse effects have been observed in other patients treated with EGF receptor-targeted therapies. In a phase II trial of the EGF receptor tyrosine kinase inhibitor OSI-774, a maculopapular acneiform rash was observed in 78% of patients.[6] In addition, cancer patients treated with C225 (cetuximab), an anti-EGF receptor monoclonal antibody, developed an acneiform follicular eruption very similar to that seen in patients treated with ZD1839.[7,8] In patients treated with ZD1839 it has been reported that the frequency of development of the pustular eruption is dose-dependent.[9] These observations support our conclusion that the cutaneous adverse effects seen in these patients are not primarily immunologically mediated but represent the results of inhibition of EGF receptor signal transduction in epidermal and follicular epithelium. This cutaneous reaction pattern therefore reflects the significance of the EGF signalling pathway in skin.

In human skin the EGF receptor is expressed by basal epidermal keratinocytes, outer root sheath cells and sebocytes.[10] Its activation by several keratinocyte-derived ligands stimulates proliferation and reduces the susceptibility to apoptosis.[11] Furthermore, in the epidermis activation of the EGF receptor reduces the terminal differentiation capacity of basal keratinocytes, but promotes differentiation of suprabasal keratinocytes.[12] Inhibition of the EGF receptor tyrosine kinase *in vitro* induces human keratinocyte growth arrest and terminal differentiation.[13] The epidermal alterations demonstrated in our patients, clinically apparent as diffuse fine scaling, are consistent with these *in vitro* findings in that they reflect a disturbance of the equilibrium between proliferation and differentiation.

In the hair follicle the EGF receptor-ligand system has an essential role in regulation of the hair cycle, as activation of the EGF receptor stimulates transition from anagen to catagen.[14] Mice harbouring a targeted disruption of the EGF receptor allele display short and wavy hair that becomes progressively atrophic, eventually resulting in alopecia.[15,16] The hair follicles in these mice do not progress from anagen to telogen and are specifically destroyed by an inflammatory infiltrate. The hair growth abnormalities and folliculitis observed in some patients treated with ZD1839 display an analogy to the findings in these transgenic mice and could thus result from inhibition of hair cycle progression. However, the precise mechanism by which inhibition of EGF receptor signalling induces a purulent folliculitis has yet to be elucidated.

The follicular eruption induced by ZD1839 has many similarities with acne vulgaris and we therefore decided to treat it empirically with tretinoin cream in two patients and minocyclin in one patient. The follicular eruption responded favourably to both of these treatments, although application of tretinoin cream worsened the scaling of the skin.

Further studies are warranted to elucidate the mechanisms by which EGF receptor-targeted therapies, such as ZD1839, induce this cutaneous reaction,

firstly to permit a more natural approach to its treatment and secondly because it could provide information on the physiological role of EGF receptor signalling in human skin. In addition, the possible use of ZD1839 in the treatment of skin diseases in which activity of the EGF receptor-ligand system is increased, such as certain skin tumours and psoriasis, deserves further attention.

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